DEPARTMENT OF HEALTH & HUMAN SERVICES

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Food and Drug Administration

466 Fernandez Juncos Avenue
Puerta De Tierra
San Juan, Puerto Rico 00901-3223

April 17, 2002

WARNING LETTER
SJN-02-09

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. Fred Hassan
Chief Executive Officer
Pharmacia
Peapack World Headquarters
100 Route 206 North
P.O. Box 800
Peapack, NJ 07977

Dear Mr. Hassan:

During an inspection of your drug manufacturing subsidiary, Searle & Co., Inc., located at 99 Jardines Street, Caguas, Puerto Rico, conducted on October 29 to December 14, 2001, our investigators documented deviations from the Good Manufacturing Practice (CGMP) regulations for drug products, Title 21, Code of Federal Regulations (21 CFR), Parts 210 and 211. These deviations cause the drug products manufactured, packaged, held and/or distributed by your firm, including oral contraceptives such as Cytotec, Arthrotec and Novo Misoprostol to be adulterated within the meaning of Section 501 (a)(2)(B) of the Federal Food, Drug and Cosmetic Act (the Act). In addition, our investigators documented various instances in which your firm failed to submit timely NDA field alert reports to the San Juan District Office, as required by 21 CFR 314.81.

The CGMP violations documented during our inspection include:

1. Failure of your quality control unit to exert its responsibility and authority as required by 21 CFR 211.22 to assure that investigations of laboratory testing results, that may impact on the identity, strength, purity, and/or safety of the drug products are completed in a timely manner, and corrective actions are carried out when necessary. For example:

    a. Cytotec 100 µg tablets investigations reviewed and related to the presence of an unknownpeak failed to clearly determine the actual source of the contamination found in at least 13 lots. An investigation dated 12/5/97, and signed on 1/22/98, suggested that the origin of the additional peak could be related to a contamination during handling. Another investigation dated]

5/12/99, suggested that the peaks found in lots [redacted] and [redacted], at a Relative Retention Time 0.59, corresponded to Toluene. This investigation of 5/12/99, indicated that a visit to the packaging line would be made to try to point out the possible source of the contamination. However, it was not until the issue was brought to your attention during the current inspection that addendums to the investigation dated 11/14/01, 11/19/01 and 11/20/01, were made. On this occasion your evaluation revealed that the most probable source of the toluene, identified in the Misoprostol assay, was related to the ink used in the Siebler I blister packaging line.

In your response to the FDA-483 (List of Inspectional Observations) a different source of the contamination was identified. Your response indicates that toluene is not a foreign substance to this product as it is used in the chemical synthesis for the Misoprostol oil. No records related to this new finding were provided to the investigators during the inspection or submitted in your response for evaluation. The records reviewed also fail to clearly demonstrate that the source of the toluene was due to a contamination caused by improper handling, the packaging line ink or residues from the active drug substance. The records fail to indicate the expected recovered percentage of toluene from the chemical synthesis and the amount expected from any other sources. Furthermore, there is no indication that toluene is being monitored during the stability of your drug substance.

b. Failure to determine in a timely manner the source of the Diethlphthalate (DEP) found in the batches of Cytotec and Arthrotec released to the market since 1999 and that were found out of specifications for DEP. Batches distributed since 1999, showed the presence of an unknown peak, identified on July 2000 as Diethlphthalate (DEP). However, it was not until the most recent inspection that ended on 12/01, that the source of the DEP was identified as the desiccant cartridge [redacted].

An investigation dated 11/01, indicates that Cytotec lots [redacted] and [redacted] showed a peak believed to be DEP, with an area percent greater than 2%, relative to the Misoprostol peak area. This investigation indicates that the source of the contaminant is currently being investigated.

c. Investigation Report No. IR 01-0112 lacks sufficient evidence to support the conclusion which points as the most probable of the unknown peaks found in Trivora lot #[redacted] as a contamination of the stainless steel needles used. The records reviewed indicate that the needles evaluated as part of the

investigation were not the same needles used during the analysis of the above lot. In addition, information provided to the investigators, related to this investigation was also contradictory.

2. Failure to assure that all tests are in conformance with the established specifications and that these are met prior to the release of drug products for distribution in accordance with 21 CFR 211.160 (2) and 211.165. For example:

   The records show a failure to test 5 batches of Norinyl 1 + 35 (Norethindrone and EthinylEstradiol) granulation (in-process) for assay [redacted], as committed under NDA-[redacted] Three of theses five batches were packaged and released to the market without the required test.

3. To assure that NDA field alerts are submitted to FDA in within 3 working days as required by 21 CFR 314.81(b)(1). Examples are as follows:

   a. Since 1997, at least thirteen batches of Cytotec tablets (Misoprostol), have shown the presence of an unknown substance during three or more stability intervals. Other records collected during the inspection show that several stability lots of Cytotec tablets presented under an investigation dated 7/6/00, showed an unknown peak in the chromatography for the assay test at approximately 3.8 minutes exceeding the 2% limit. Field Alert Reports were not submitted to FDA for either of the incidents related to unknown peaks found in Cytotec manufactured since 1997 to present.

   b. Records reviewed show that during the stability studies of Arthrotec (75 mg Diclophenac/200 µg Misoprostol) and Novo-Misoprostol (200 µg Misoprostol) tablets, the presence of an unknown contaminant peak was found exceeding the established specifications. Although the source of the contaminant was later identified to be the desiccant cartridge, no FAR was submitted to FDA.

Your written response to the FDA-483 (List of Inspectional Observations) appears to adequately address the deficiencies listed, with the exception of the issues discussed below. Similar deficiencies were reported to your firm in a Warning Letter, SJN-97-03, dated 1/31/97. Your firm's response to that Warning Letter also made adequate commitment for corrective action. We consider the recurrence of the deficiencies found during our most recent inspection to be recidivist.

The records reviewed and the comments included in your response regarding the presence of the unknown peaks, fails to include an evaluation of all the marketed lots to assure that these are in conformance to the established specifications for impurities. We concur with the investigators that an evaluation of all lots released to the market, that may be affected by the presence of this or any other contaminant found, is necessary to assure compliance with the NDA commitments and the regulations.

In addition, none of the records collected during the inspection or provided with your response shows an acceptable justification for not submitting NDA Field Alert Reports as required at the moment of detecting these unknown peaks exceeding the specifications.

The above identification of violations is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to assure adherence with the requirement of the Good Manufacturing Manufacturing Practice Regulations. Federal agencies are advised of the issuance of all warning letters about drugs so that they may take this information into account when considering the award of contracts.

Please notify the San Juan District Office, in writing, within 15 working days of receipt of this letter, of the specific steps you have taken to correct the noted violations, including an explanation of each step being taken to prevent recurrence of these or similar violations.

Also include in your response your evaluation and list of the marketed lots of Cytotec and Aristotec that may be affected by the presence of Toluene, DEP or any unknown substance found above the established specifications.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. These include seizure and/or injunction.

Your reply should be sent to the Food and Drug Administration, San Juan District Office, 466 Fernández Juncos Ave., San Juan, Puerto Rico 00901-3223. Attention: Carmelo Rosa, Compliance Officer

Sincerely,

Mildred R. Barber
District Director

cc: Anita Marchand, Plant Manager
Searle & Co., Inc.
P.O. Box 363826
San Juan, PR 00936-3826